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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 February 2001 (05.02.01)	
International application No. PCT/SE00/01138	**Applicant's or agent's file reference** L45 P3PCT
International filing date (day/month/year) 31 May 2000 (31.05.00)	**Priority date** (day/month/year) 01 June 1999 (01.06.99)
Applicant ERIKSSON, Tomas	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 December 2000 (08.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Catherine Massetti
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference L45 P3PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE00/01138	International filing date *(day/month/year)* 31.05.2000	Priority date *(day/month/year)* 01.06.1999
International Patent Classification (IPC) or national classification and IPC: A 61 K 38/09		
Applicant Läkartjänster i Västsverige et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.12.2000	22.05.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket S-[illegible] STOCKHOLM Telex 17976 PATORE S-S Facsimile No. 08-667 72 88	Authorized officer Hampus Rystedt/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01138

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language English which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☒ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-4	YES
	Claims		NO
Inventive step (IS)	Claims	1-4	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-4	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present application relates to the use of GnRH-analogues for the production of a pharmaceutical preparation for diagnosis of Obsessive Compulsive Disorder, OCD, and estimating the severity of the disease. The preparation may be administered intravenously or via a nasal spray.

The use of GnRH-tests, i.e. administration of GnRH-analogues and measuring levels of gonadotropic hormones in the blood, is well known in art, However, the test has never been shown to be applicable to the diagnosis of OCD. Claims 1-4 are therefore novel and considered to possess inventive step. They are also considered to be industrially applicable.

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SÄNT MED FAX
2000 -05- 31

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/SE 00 / 01138

International Filing Date 2000 -05- 31

The Swedish Patent Office
PCT International Application

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* L45 P3PCT

Box No. I TITLE OF INVENTION

Diagnostics of OCD

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Läkartjänster i Västsverige AB
Box 71
SE-427 22 Billdal
Sweden

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: Sweden

State *(that is, country)* of residence: Sweden

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ROISE

Tomas Eriksson
Box 71
SE-427 22 Billdal
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: Sweden

State *(that is, country)* of residence: Sweden

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below ~~is hereby~~/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Anyone of BERGENTALL Annika; CEDERBOM Hans; GUSTAFSSON Leif; BURÖ Peter
of
Cegumark AB
Box 53047, S-400 14 Göteborg,
Sweden

Telephone No. +46-31-600 700

Facsimile No. +46-31-600 725

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AE** United Arab Emirates
- [X] **AL** Albania
- [X] **AM** Armenia
- [X] **AT** Austria
- [X] **AU** Australia
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia and Herzegovina
- [X] **BB** Barbados
- [X] **BG** Bulgaria
- [X] **BR** Brazil
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- [X] **CA** Canada
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- [X] **CN** China
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- [X] **CZ** Czech Republic
- [X] **DE** Germany
- [X] **DK** Denmark
- [X] **DM** Dominica
- [X] **EE** Estonia
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- [X] **FI** Finland
- [X] **GB** United Kingdom
- [X] **GD** Grenada
- [X] **GE** Georgia
- [X] **GH** Ghana
- [X] **GM** Gambia
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- [X] **HU** Hungary
- [X] **ID** Indonesia
- [X] **IL** Israel
- [X] **IN** India
- [X] **IS** Iceland
- [X] **JP** Japan
- [X] **KE** Kenya
- [X] **KG** Kyrgyzstan
- [X] **KP** Democratic People's Republic of Korea
- [X] **KR** Republic of Korea
- [X] **KZ** Kazakhstan
- [X] **LC** Saint Lucia
- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MA** Morocco
- [X] **MD** Republic of Moldova
- [X] **MG** Madagascar
- [X] **MK** The former Yugoslav Republic of Macedonia
- X **MZ** Mozambique
- [X] **MN** Mongolia
- [X] **MW** Malawi
- [X] **MX** Mexico
- [X] **NO** Norway
- [X] **NZ** New Zealand
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- [X] **SI** Slovenia
- [X] **SK** Slovakia
- [X] **SL** Sierra Leone
- [X] **TJ** Tajikistan
- [X] **TM** Turkmenistan
- [X] **TR** Turkey
- [X] **TT** Trinidad and Tobago
- [X] **TZ** United Republic of Tanzania
- [X] **UA** Ukraine
- [X] **UG** Uganda
- [X] **US** United States of America
- [X] **UZ** Uzbekistan
- [X] **VN** Viet Nam
- [X] **YU** Yugoslavia
- [X] **ZA** South Africa
- [X] **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [X] **DZ** Algeria
- [X] **AG** Antigua and Barbuda

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 1 June 1999 01/06/99	9902026-5	Sweden		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 3
description (excluding sequence listing part)	: 6
claims	: 1
abstract	: 1
drawings	: 1
sequence listing part of description	:
Total number of sheets	: 12

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Copy of Official Action SE9902026-5

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: Swedish

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Göteborg, May 30, 2000

Leif Gustafsson

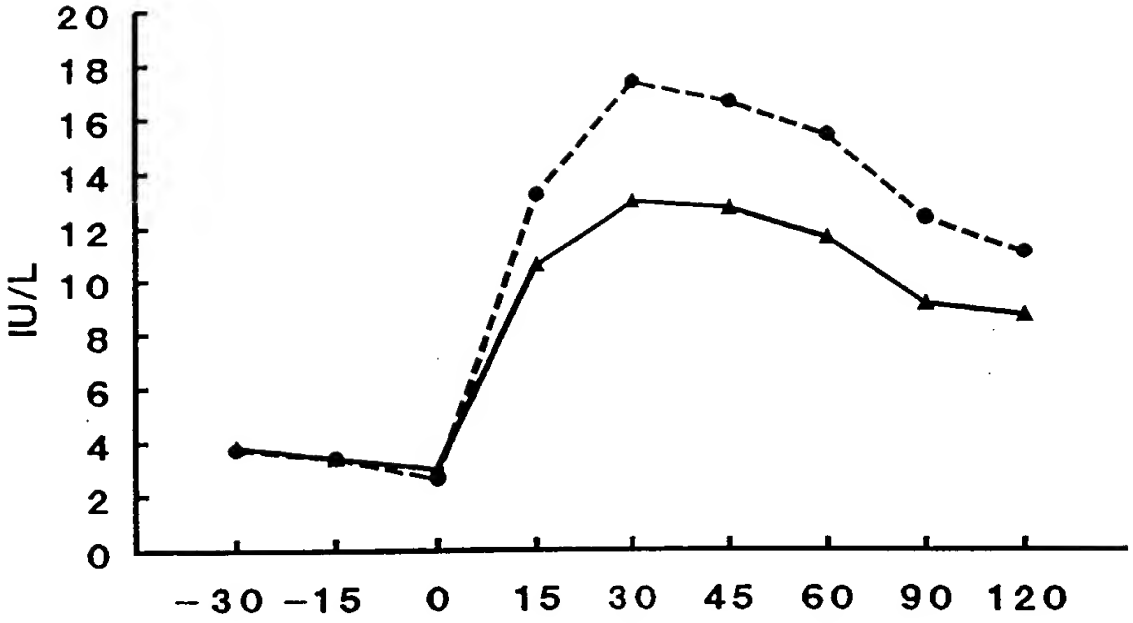
For receiving Office use only

1. Date of actual receipt of the purported international application:	2000 -05- 31
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/SE	6. ☐ Transmittal of search copy delayed until search fee is paid.

2. Drawings: ☒ received: ☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau: 30 JUNE 2000 (30.06.00)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L45 P3 SE, 1999-06-01

TITEL

Läkemedel för diagnostik av tvångstanke-tvångshandlingssjukdom

TEKNISKT OMRÅDE

Föreliggande uppfinning avser ett läkemedel för diagnostik av tvångstanke-tvångshandlingssjukdom (OCD; obsessive-compulsive disorder).

UPPFINNINGENS BAKGRUND

Sjukdomen OCD

OCD är en kronisk psykiatrisk sjukdom där de huvudsakliga symptomen utgöres av att patienten har tvångsmässigt kommande tankar som han/hon inte kan styra bort och som på ett ofta plågsamt och destruktivt sätt hindrar honom/henne från att tänka på andra saker eller att patienten på ett tvångsmässigt sätt utför rituella handlingar som blockerar möjligheterna för honom/henne att ägna sig åt andra aktiviteter. Sjukdomen är vanligtvis kronisk och ofta av så allvarlig grad att patienten är helt eller partiellt arbetsoförmögen.

Sjukdomen beskrivs och definieras detaljerat i The Diagnostic and Statistical Manual of Mental Disorders, fjärde upplagan (DSM-IV) utgiven av American Psychiatric Association 1994.

Vetenskapens nuvarande ståndpunkt vad gäller diagnostik av sjukdomen OCD

I klinisk praxis diagnostiseras sjukdomen på basen av patientens uppgifter om aktuella symptom. Någon objektiv metod för

diagnostik av sjukdomen eller bedömning av dess allvarlighetsgrad finns på vetenskapens nuvarande ståndpunkt icke.

Fysiologisk reglering av androgena hormoner under normala förhållanden (d v s utan påverkan av läkemedel)

I en viss del av hjärnan bildas ett hormon - gonadotropin releasing hormone (GnRH).

GnRH - i sin tur - stimulerar bildningen av s k gonadotropiner i hypofysen (på hjärnans undersida). De kända gonadotropinerna hos människa är luteiniserande hormon (LH) och follikelstimulerande hormon (FSH). Dessa hormoner frisättes till blodet och transporteras till testiklarna och binjurarna (hos mannen) och till äggstockarna (ovarierna) och binjurarna (hos kvinnan). I dessa körtlar stimulerar gonadotropinerna till bildning av flera olika hormoner däribland de s k androgenerna (de manliga könshormonerna) av vilka testosteron är den vanligaste.

De androgena hormonerna frisättes till blodet från de körtlar där de producerats. De transporteras med blodet till olika organ där de utövar sina många olika effekter. Ett av dessa organ är hjärnan. De androgena hormonerna utövar sin effekt i hjärnan genom att bindas till och stimulera s k receptorer i vissa delar av hjärnan. Avgörande för hur stark androgen aktivitet som skall komma att utvecklas är dels mängden androgent hormon i blodet, dels täthet och känslighet i de receptorer till vilka de androgena hormonerna binder sig. Den androgena aktiviteten kan alltså vara hög såväl vid en hög koncentration av androgent hormon i blodet som vid en hög täthet och/eller känslighet hos de androgena receptorerna.

Bildandet av androgena hormoner är normalt underkastad en s k "feed-back" reglering. Om den androgena aktiviteten i hjärnan är hög sker en kompensatorisk minskning i bildandet av gonadotropiner med en ity åtföljande minskning av bildandet av androgena hormoner. Om en hög androgen aktivitet i hjärnan beror på att receptorerna har hög täthet och/eller känslighet (och ej på att halten av androgena hormoner i blodet är hög) kan den kompensatoriska feed-back-regleringen leda till att bildandet av androgena hormoner sjunker till en onormalt låg nivå utan att detta i sig är ett tecken på att den androgena aktiviteten är låg; den kan fortfarande vara hög (om kompensationen inte varit tillräcklig) eller normal (om kompensationen varit tillräcklig).

S k GnRH-analoger

Detta är ämnen som till sin verkan efterliknar det kroppsegna GnRH (gonadotropin releasing hormone), d v s de stimulerar frisättningen av gonadotropiner från hypofysen till blodet. GnRH-analoger används som läkemedel med två syften. För det första används de för att minska den androgena aktiviteten vid t ex prostatacancer. Det sker genom en nedreglering i känsligheten i de receptorer på vilka naturligt GnRH och GnRH-analoger verkar. En sådan nedreglering uppkommer efter en tids behandling med en åtföljande hämning av androgenbildningen som följd.

För det andra används de vid diagnostik av vissa somatiska sjukdomar medelst det s k GnRH-testet (se nedan).

GnRH-test

Vid vissa endokrinologiska sjukdomar föreligger en ändrad känslighet och/eller täthet i GnRH-receptorerna i CNS. Detta kan undersökas med hjälp av det s k GnRH-testet i vilket en liten

mängd av en GnRH-analog injiceras intravenöst i blodbanan. Med korta tidsintervaller efter injektionen tages blodprover i vilka koncentrationen av LH och/eller FSH mäts. Under normala förhållanden sker hos friska en ökad frisättning av LH och FSH efter injektion av en GnRH-analog. Vid olika endokrina sjukdomar ses avvikelser i LH- och/eller FSH-frisättningen efter injektion med en GnRH-analog. Härigenom kan en avvikande känslighet i GnRH-receptorerna påvisas. Användning av denna diagnostikmetod beskrivs exempelvis i Hormone Res. 6: 177-191 (1975), P. Franchimont m.fl.

TEKNISKA PROBLEMET

Ändamålet med föreliggande uppfinning är att åstadkomma ett läkemedel som gör det möjligt att diagnostisera och bedöma intensiteten av den psykiatriska sjukdomen OCD, genom användning av ett diagnostiskt test med detta läkemedel.

LÖSNINGEN

Enligt uppfinningen kan detta uppnås genom användning av komposition omfattande minst ett ämne inom gruppen GnRH-analoger för framställning av ett läkemedel för diagnostik av tvångstanke-tvångshandlingssjukdom (OCD; Obesessive-compulsive disorder).

BESKRIVNING AV RITNING

Uppfinningen kommer nedan att beskrivas med hänvisning till en bifogad ritning som visar resultat från test på patienter och friska kontrollpersoner.

BESKRIVNING AV UTFÖRINGSEXEMPEL

Den nedan beskrivna diagnostiska metoden har sin intellektuella grund i en kombination av observationer som gjorts i patientkontakter på en psykiatrisk specialistmottagning i Göteborg, och vetenskapligt kända fakta. Härutöver grundar sig metoden på ett vetenskapligt utfört experiment. Sammanfattningsvis gäller det följande observationer och fakta.

1. Det har nyligen upptäckts att sjukdomen OCD effektivt kan behandlas med långverkande analoger till gonadotropin frisättande hormoner (GnRH). Denna observation utgör belägg för att den androgena aktiviteten i centrala nervsystemet (CNS) av någon anledning är ökad vid OCD. Eftersom koncentrationen av androgena hormoner i blodet ej har visat sig vara ökad vid OCD måste i stället känsligheten och eller tätheten hos de receptorer i CNS, vilka stimuleras av de androgena hormonerna, vara ökad. En sådan ökad hormonell aktivitet leder, enligt kända fysiologiska principer, till att insöndringen av det stimulerande hormonet genom "feed-back"- reglering minskas. I detta fall skulle en sådan "feed-back" reglering kunna medieras av GnRH genom en minskad insöndring av detta hormon. En sådan minskad insöndring bör, enligt kända fysiologiska principer, leda till en ökad känslighet i GnRH-receptorerna i CNS.

2. I ett vetenskapligt experiment har sex patienter med en svår form av OCD undersökts med det s k GnRH-testet. För jämförelse undersöktes fem friska kontroller. I detta experiment visade det sig att frisättningen av LH efter injektion av en GnRH-analog var större hos patienterna med OCD än hos kontrollpersonerna. Detta fynd styrker hypotesen

att det föreligger en ökad känslighet i GnRH-receptorerna hos patienter med OCD och visar att det inom somatisk sjukvård använda GnRH-testet kan användas i diagnostiken av denna psykiatriska sjukdom.

Ritningen visar i diagramform resultat av GnRH-test på patienter som lider av sjukdomen OCD samt på en jämförelsegrupp av friska kontrollpersoner. I diagrammet anger abskissan tiden i minuter, medan ordinatan anger koncentration av luteiniserande hormon (LH) i blod. Diagrammet visar det aritmetiska medelvärdet av koncentrationen av luteiniserande hormon hos dels patienter med sjukdomen OCD (streckad linje) (n=6) och dels friska kontroll-personer (heldragen linje) (n=5). Provtagning inleddes med ettförsta blodprov som 15 min. senare följdes av ett andra blodprov. Vid tidpunkten 0 (enligt diagrammet) togs ytterligare ett blodprov samt injicerades intravenöst 0.1 mg RELEFACT® LH-RH, som tillhandahålles av HOECHST MARION ROUSSEL. Blodprov togs därefter 6 gånger med intervall av 15,30,45,60,90 och 120 min. Blodproven analyserades radioimmunologiskt.

Vid statistisk beräkning med variansanalys med upprepade mätningar har resultatet från patientgruppen visat sig vara statistiskt skilt från kontrollgruppen ($F=5,6$; $p<0,05$). Skillnaden mellan de båda grupperna är således signifikant. Individuella skillnader inom patientgruppen tyder dessutom på att patienter som uppvisar stor känslighet (hög koncentration av LH i blodet) med avseende på denna diagnostik, även uppvisar en högre sjukdomsintensitet. Det ovan beskrivna läkemedlet kan således användas för att förbättra diagnostiken av OCD och därmed underlätta för personer som lider av OCD att få en adekvat behandling.

L45P3SE, 1999-06-01

PATENTKRAV

1. Användning av komposition omfattande minst ett ämne inom gruppen GnRH-analoger för framställning av ett läkemedel för diagnostik av tvångstanke-tvångshandlingssjukdom (OCD; Obesessive-compulsive disorder).

2. Användning enligt kravet 1, varvid läkemedlet ingår i en beredning som är avsedd för administration genom intravenös injektion.

3. Användning enligt kravet 1, varvid den ingår i en beredning som är avsedd för administration genom nässpray.

4. Användning av komposition omfattande minst ett ämne inom gruppen GnRH-analoger för framställning av ett läkemedel för bedömning av allvarlighetsgraden av en tvångstanke-tvångshandlingssjukdom (OCD;Obesessive-compulsive disorder).

SAMMANDRAG

Uppfinningen avser ett läkemedel för diagnos av tvångstanke-tvångshandlingssjukdom (OCD; Obesessive-compulsive disorder). Uppfinningen gör det möjligt för patienter med OCD att erhålla en säkrare diagnos samt en indikation på sjukdomens intensitet.

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(54) Title: USE OF A PHARMACOLOGICAL AGENT IN THE DIAGNOSIS OF OBSESSIVE-COMPULSIVE DISORDER

(57) Abstract: The invention relates to the use of a pharmacological agent for diagnosis of OCD; Obsessive-compulsive disorder. The invention makes it possible for patients suffering from OCD to obtain a more accurate diagnosis and an indication on the intensity of the disorder.

TITLE

Use of a pharmacological agent in the diagnosis of obsessive-compulsive disorder.

TECHNICAL FIELD

The present invention relates to the use of a pharmacological agent in the diagnosis of obsessive-compulsive disorder (OCD).

THE BACKGROUND OF THE INVENTION

Obsessive-compulsive disorder

OCD is a chronic psychiatric disease where the main symptoms are constituted by the patient having compulsive thoughts that he/she can not fend off and which often in a painful and destructive way prevents the person from thinking of other things or that the patient in a compulsive manner performs ritual acts that block the possibility for the person to devote herself or himself to other activities. The disorder is usually chronic and often so serious that the patient is completely or partially incapacitated.

The disorder is described and defined in detail in The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) published by the American Psychiatric Association in 1994.

State of the art in the diagnosis of OCD

In the clinic the disorder is diagnosed on the basis of information given by the patient on the present symptoms. At the present state of the art of science no objective method for the diagnosis of the disorder or for the estimation of its severity is available.

Physiological regulation of androgenic hormones under normal conditions (i.e. without influence of drugs)

A hormone - gonadotropin releasing hormone (GnRH) is produced in a certain part of the brain. GnRH - in its turn - stimulates the production of so called gonadotropins in the pituitary (at the bottom of the brain). In man the gonadotropins are the luteinizing (LH) hormone and the follicle-stimulating hormone (FSH). These hormones are released to the blood and transported to the testes and the adrenal glands (of the male) and to the ovaries and the adrenal glands (of the female). In these glands the gonadotropins stimulate the synthesis of several different hormones among them the so called androgens (the male sex hormones) of which testosterone is the most common.

The androgenic hormones are released to the blood from the glands in which they are produced. They are transported with the blood to different organs where they exert their various actions. One of these organs is the brain. The androgenic hormones exert their effects in the brain by binding to and stimulating so called receptors in certain parts of the brain. The determining factor for how strong androgenic activity that will be exerted, is on one hand the amount of androgenic hormone in the blood, on the other the density and sensitivity of the receptors to which the androgenic hormones bind. The androgenic activity may thus be high, both at a high concentration of androgenic hormone in the blood, as well as in case of a high density and/or sensitivity of the androgenic receptors.

The synthesis of androgenic hormones is normally subjected to a so called "feed-back" regulation. If the androgenic activity in the brain is high, a compensating decrease in the release of gonadotropins takes place with an accompanying reduction of the

production of androgenic hormones. At a high androgenic activity in the brain owing to a high density and/or sensitivity of the receptors (and not due to the content of androgenic hormones in the blood being high), the compensating feed-back-regulation may lead to a decreased production of androgenic hormones causing abnormally low level, without this in itself being a sign that the androgenic activity being low; it may still be high (if the compensation has not been sufficient) or normal (if compensation has been sufficient).

So-called GnRH-analogues

These are substances that in their effects resemble the endogenously produced GnRH (gonadotropin releasing hormone), that is they stimulate the release of the gonadotropins from the pituitary to the blood. The GnRH-analogues are used as pharmacological agents for two purposes. First, they are used to reduce the androgenic activity for example in cases of cancer of the prostate. This is achieved by a down-regulation in the sensitivity in those receptors on which endogenous GnRH and analogues of GnRH act. Such a down-regulation is established after treatment during a certain period of time with a subsequent inhibition of the synthesis of androgens.

Secondly, they are used in the diagnosis of certain somatic disorder by means of the so-called GnRH-test (see below).

The GnRH-test

A deviant sensitivity and/or density in the GnRH receptors in CNS is present in certain endocrine disorders. Such deviations could be investigated with the so-called GnRH-test in which a small amount of an analogue of GnRH is injected intravenously. Blood samples are collected with short time intervals after the injection in which the concentrations of LH and/or FSH are

determined. Under normal conditions, an increased release of LH and FSH is seen in healthy subjects after an injection of an analogue of GnRH. In various endocrine diseases, deviations in the release of LH and/or FSH after the injection with a analogue of GnRH is seen. By this procedures, a deviant sensitivity in the GnRH-receptors could be demonstrated. The use of this diagnostic method is, for example, described in Hormone Res. 6:177-191 (1975), P. Franchimont et al.

THE TECHNICAL PROBLEM

The objective of the present invention is to provide a pharmaceutical composition which enables the diagnosis and the assessment of the severity of the psychiatric disorder OCD by the use of a diagnostic test with this composition.

THE SOLUTION

For this object, the invention is characterised in that the composition comprises at least one substance within the group GnRH-analogue for the production of a pharmacological agent for the diagnosis of obsessive-compulsive disorder (OCD).

DESCRIPTION OF A DRAWING

The invention will be described with reference to a drawing which is enclosed and which demonstrates the results from investigations of patients and healthy control subjects.

DETAILED DESCRIPTION OF PERFORMED EXAMPLES OF THE INVENTION

The diagnostic method, described below, has its intellectual basis in a combination of observations made in contacts with patients on a specialised psychiatric clinic in Göteborg, and established scientific facts. In addition to that, the method is based on a scientific experiment.

To sum up, it has reference to the following observations and facts.

1. It was recently discovered that the disorder OCD could effectively be treated with a long-acting analogue of the gonadotropin-releasing hormone (GnRH). That observation demonstrates that the androgenic activity in the central nervous system (CNS), for some reason, is increased in OCD. Since the concentration of androgenic hormones in blood not has been shown to be increased in OCD, the sensitivity and/or the density of those receptors in CNS, which are stimulated by the androgenic hormones, must be increased. Such an increased hormonal activity causes, according to well-known physiological principles, by a feed-back regulation, a decrease in the release of the stimulating hormone. In the present case, a feed-back regulation might be mediated via GnRH by a decreased release of this hormone. Such a decreased release should, according to well-known physiological principles, cause an increase in the sensitivity in the GnRH-receptors in CNS.

2. In a scientific experiment six patients, all suffering from a severe form of OCD, have been examined by the so-called GnRH-test. For comparison, five healthy controls were examined. This experiment showed that the release of LH, after the injection of an analogue of GnRH was more pronounced in the patients suffering from OCD than in the control subjects. This finding strengthens the hypotheses that there is an increased sensitivity in the GnRH-receptors in patients with OCD and it shows that the GnRH-test, used within somatic medical care, could be used in the diagnosis of this psychiatric disorder.

The drawing shows, as a graph, the result of the GnRH-test in patients suffering from the disorder OCD and in a comparison

group of healthy control subjects. In the graph, the abscissa gives the time in minutes and the ordinate the concentration of luteinizing hormone (LH) in blood. The graph show the arithmetic mean of the concentration of luteinizing hormone in patients suffering from the disorder OCD (broken line)(n=6) and in healthy control subjects (solid line)(n=5). The collection of blood samples started with a first blood sample which 15 min later followed by a second sample. At the time point 0 (according to the graph) still one blood sample was collected and 0.1 mg Relefact® LH-RH, which is commercially available from Hoechst Marion Roussel, was injected intravenously. After that, blood samples were collected 6 times with intervals of 15, 30, 45, 60, 90, and 120 min. The blood samples were analysed with a radioimmunologic technic.

In a statistical assessment by means of a analysis of variance for repeated measures the results obtained from the group of patients have shown to be statistically different from the control group ($F=5.6$; $p<0.05$). Thus, the difference between the two groups is significant. Furthermore, individual differences within the patient group indicate that patient who show a high sensitivity (high concentration of LH in the blood) in this diagnostic test also show a higher intensity of the disorder. Thus, the pharmacological agent described above, could be use to improve the diagnosis of OCD and thus make it easier for people suffering from OCD to receive an adequate treatment.

CLAIMS

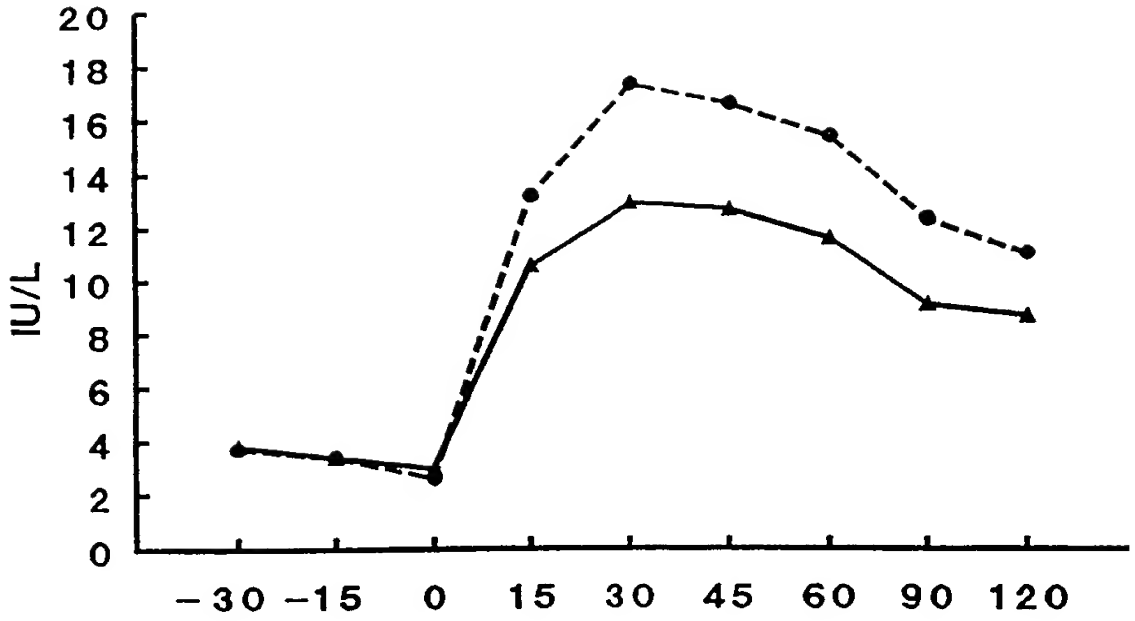
1. Use of a composition comprising at least one substance within the group GnRH analogues for producing a pharmacological agent for the diagnosis of OCD (obsessive-compulsive disorder).

2. Use according to claim 1, wherein the pharmacological agent is a part of a preparation which is intended for administration by means of intravenous injection.

3. Use according to claim 1, wherein the pharmacological agent is a part of a preparation which is intended for administration by means of a nasal spray.

4. Use of a composition comprising at least one substance within the group GnRH analogues for producing a

5. for the assessment of the degree of severity of a certain case of OCD; obsessive-compulsive disorder.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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BRITISH JOURNAL OFPSYCHIATRY, Volume 173, 1998, T. ERIKSSON, "Anti-androgenic agent cyproterone acetate cured a woman of severe sexual obsessions", page 351 ---	1-4
A	Acta psychiatr.scand., Volume 73, 1986, M. Casas et al, "Antiandrogenic treatment of obsessive-compulsive neurosis" page 221 - page 222 --- --------	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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